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Stereoselective Formation of α-Fluoro-α-trifluoromethyl-γ-lactones Starting from γ-Hydroxy-α,β-unsaturated Sulfones and a Hexafluoropropene-Diethylamine Adduct (PPDA)

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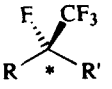
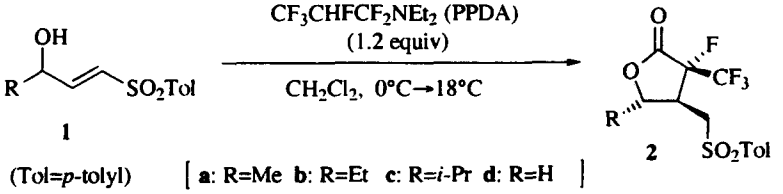
Abstract : (*E*)-3-Hydroxy-1-alkenyl *p*-tolyl sulfones (**1**) reacted with a hexafluoropropene-diethylamine adduct (PPDA) to afford α-fluoro-α-(trifluoromethyl)-β-[(*p*-tolylsulfonyl)methyl]-γ-lactones (**2**). This reaction is so stereoselective that only one diastereomer of **2** is detected in the reaction mixture. A plausible mechanism for this intriguing reaction is discussed. © 1997 Elsevier Science Ltd.

Fluorinated organic compounds are well known to usually show unique chemical and biological properties so that many types of the functionalities involving fluorine atom(s) are utilized for useful materials such as biologically active compounds,[1] ferroelectric liquid crystals,[2] and piezoelectric materials.[3] Up to date, various methods have been developed for introducing fluorine atom(s) into organic molecules, and some excellent papers have appeared for the preparation of fluoro(trifluoromethyl)methylene-containing compounds (**A**) and their utilization.[4] Here we wish to describe a novel, stereospecific formation of α-fluoro-α-trifluoromethyl-β-(*p*-tolylsulfonyl)methyl-γ-lactones (**2**), which have a fluoro(trifluormethyl)-methylene moiety, starting from (*E*)-γ-hydroxy-α,β-unsaturated sulfones (**1**). Notably, optically active γ-lactones (**2**) can be prepared by the present reaction (*vide infra*). Since the γ-lactones (**2**) possess a *p*-tolylsulfonyl group and a reactive carbonyl group adjacent to strong electron-withdrawing F and CF_3 groups, the present reaction is anticipated to open a novel synthetic route to many kinds of fluoro(trifluoromethyl)-methylene-containing materials.



(**A**)

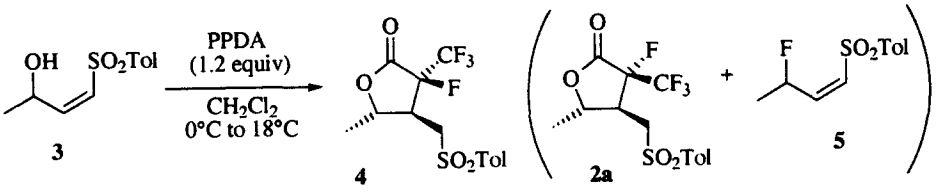


1 **2**

(Tol=*p*-tolyl) [**a**: R=Me **b**: R=Et **c**: R=*i*-Pr **d**: R=H]

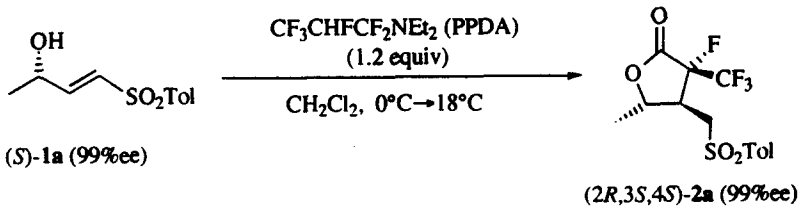
In order to prepare 3-fluoro-1-butenyl *p*-tolyl sulfone, we treated (*E*)-3-hydroxy-1-butenyl *p*-tolyl sulfone (**1a**) with a hexafluoropropene-diethylamine adduct (PPDA) which can be utilized as a reagent for fluorinating some alcohols.[5] To our surprise, the substitution of the hydroxyl group by the fluorine atom did not occur, but γ-lactone **2a** was produced. Interestingly, the reaction was stereospecific enough to give only one diastereomer of **2a**. To a solution of **1a** (1.0 mmol) in dry dichloromethane (10 ml), a solution of PPDA (1.2 mmol) in dry dichloromethane (2 ml) was dropwise added over 15 min under ice-cooling. The resulting solution was stirred for 3.5 h at 18 °C. The reaction was quenched with water (5 ml) and extracted with dichloromethane. The organic layer was dried ($MgSO_4$), evaporated, and chromatographed (GPC/$CHCl_3$ and silica gel column/hexane-AcOEt 2:1) to give **2a** (517 mg; 72% yield) along with the starting **1a** (16%). HPLC and ^1H NMR analyses showed that **2a** was produced as only one diastereomer. The structure of **2a** was elucidated by a single crystal X-ray crystallography:[6] The β-(*p*-Tolylsulfonyl)methyl group is located anti to the α-fluoro and γ-alkyl groups. In a similar manner, the ethyl and isopropyl analogues **2b** and **2c** were obtained in 73% and 68% yields, respectively, from the corresponding **1**. In every case, γ-lactone **2** was also produced as one diastereomer. (*E*)-3-Hydroxy-1-propenyl *p*-tolyl sulfone (**1d**) that has no alkyl substituent at its γ-position gave γ-lactone **2d** as a single diastereomer in 74% yield. The single crystal X-ray structural analysis revealed that **2d** retained the anti stereochemical relationship between the α-fluoro and β-(*p*-tolylsulfonyl)methyl groups.[6]

The present stereospecific formation of the γ-lactone ring seems to be limited to acyclic 3-hydroxyl-1-alkenyl sulfones represented by the formula **1**, which has at least one hydrogen at the γ-position. Thus, (*E*)-3-hydroxy-3-methyl-1-butenyl *p*-tolyl sulfone did not give the expected γ-lactone, but 3-fluoro-3-methyl-1-butenyl *p*-tolyl sulfone was formed in 73% yield. Similar treatment of 3-hydroxy-1-cyclohexenyl *p*-tolyl sulfone with PPDA gave 3-fluoro-1-cyclohexenyl *p*-tolyl sulfone in 62% yield.



The stereospecificity in the reaction of **1** with PPDA was confirmed by that of (*Z*)-3-hydroxy-1-butenyl *p*-tolyl sulfone (**3**). When **3** was treated with PPDA in dry dichloromethane, a new γ-lactone (**4**) was obtained as the main product (30% yield) together with **2a** (13% yield) and the fluorinated product **5** (20% yield). The stereochemistry of **4** was also assigned by X-ray crystallography.[6]

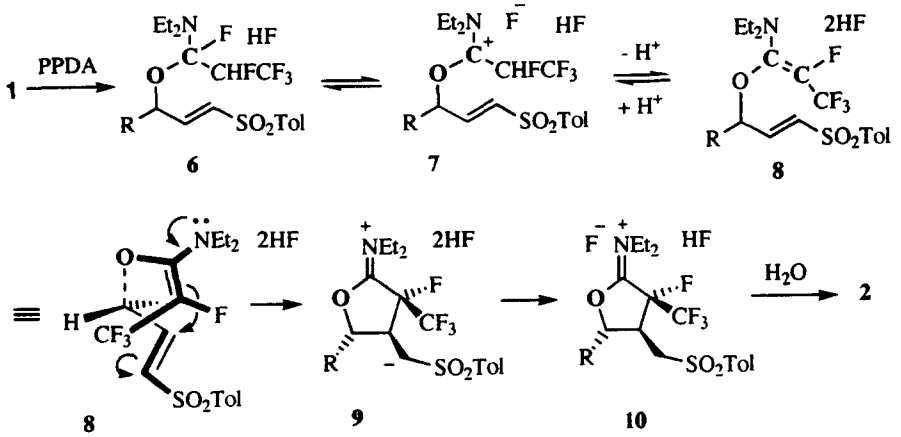
Recently, Carretero and Dominguez reported an efficient preparation of optically active γ-hydroxy-α,β-unsaturated sulfones using lipase PS-catalyzed transesterification.[7] Hence, we applied the present reaction to (*S*)-**1a** (99%ee). Fortunately, no racemization occurred and (2*R*,3*S*,4*S*)-**2a** was afforded in 73% yield with a high enantioselectivity of 99%.[8]



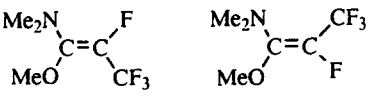
(*S*)-**1a** (99%ee)

(2*R*,3*S*,4*S*)-**2a** (99%ee)

Finally, we wish to present a plausible mechanism (Scheme 1) for the stereospecific reaction of **1** with PPDA to form the γ-lactones (**2**), although conclusive evidence for this is unavailable at the present time. The key intermediate is an enamine (**8**) that is derived from **1** and PPDA.



Scheme 1. A plausible mechanism for the formation of **2** from **1**.



(*E*)-**11** (*Z*)-**11**

Δ H_f (kcal mol^{-1})	0.0	0.9

Fig. 2. Molecular orbital calculation of a model compound (**11**)

By the molecular orbital calculation of a model enamine (**11**) with a PM3 method (Figure 2),[9] the (*E*)-geometric isomer was shown to be more stable by 0.9 kcal mol^{-1} than the (*Z*)-isomer, suggesting that the intermediary (**8**) prefers the (*E*)-geometry. In (*E,E*)-**8**, the enamino group attacks intramolecularly on the β-carbon of the α,β-unsaturated sulfone part in such a manner that the trifluoromethyl group avoids the *p*-tolylsulfonyl group. This addition gives rise to the cis relationship between the trifluoromethyl and (*p*-tolylsulfonyl)methyl groups on the newly-formed five-membered ring. The final hydrolysis (workup) of the resulting cyclization product (**10**) produces the γ-lactone (**2**).

In conclusion, we found the stereospecific formation of α-fluoro-α-(trifluoromethyl)-β-[(*p*-tolylsulfonyl)methyl]-γ-lactones (**2**) from (*E*)-3-hydroxy-1-alkenyl *p*-tolyl sulfones (**1**) by the action of

hexafluoropropene-diethylamine adduct (PPDA). Now we are investigating the nucleophilic addition of organometallic compounds to **2** in order to develop a novel method for synthesizing fluoro(trifluoromethyl)-methylene-containing materials.

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6. X-Ray crystallographic data were collected with Cu Kα (λ = 1.54178 Å) radiation on a Mac Science MXC18 diffractometer. All computations used "Crystan GM (ver 6.2.1), Computer Program for the Solution and Refinement of Crystal Structure from X-Ray Diffraction Data (1994)", Mac Science Co. Ltd..
   Crystal data of **2a** : monoclinic, space group $P2_1/n$, a = 16.258(4) Å, b = 11.406(3) Å, c = 8.706(2) Å, β = 99.99(2)°, V = 1590.0(7) Å^3, Z = 4, R = 0.0428, Rw = 0.0489.
   Crystal data of **2d** : monoclinic, space group $P2_1/n$, a = 20.093(6) Å, b = 10.318(4) Å, c = 6.921(2) Å, β = 98.62(2)°, V = 1418.7(8) Å^3, Z = 4, R = 0.0509, Rw = 0.0409.
   Crystal data of **4** : monoclinic, space group $P2_1/n$, a = 16.992(5) Å, b = 5.780(2) Å, c = 15.821(4) Å, β = 98.84(2)°, V = 153.4(9) Å^3, Z = 4, R = 0.0438, Rw = 0.0404.
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8. The enantiomeric excess was determined by HPLC using CHIRALPAK OD. (*n*-hexane:*i*-PrOH= 20:1)
9. With MOPAC (ver 6) molecular orbital package packed in Materia (ver. 2.1; Teijin System Technology, Ltd.) : Stewart, J. J. P. *QCPE* **1989**, *9*, 10.

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